Protein Structures

A protein domain is considered to be a distinct functional and/or structural unit. A domain in a structural context refers to a segment of a polypeptide chain that can fold into an independent three-dimensional structure. It may interact with other domains of the protein or may simply be joined to other domains by a polypeptide chain. A domain in a sequence context refers to a long sequence pattern that is shared by other proteins having a common evolutionary origin. A domain may include all of the protein sequence or a part of it. A conserved domain is a recurring unit in molecular evolution whose extents can be determined by sequence and structure analysis.

The Conserved Domain Database (CDD) contains domains derived from the Smart, Pfam and Clusters of Orthologous Groups (COGs) databases. Conserved domains can be represented as multiple sequence alignments. Source alignments are processed by NCBI as follows:

- Sequences in the alignment for which a link cannot be provided to a protein in Entrez are removed.
- If possible, a closely related sequence with a known structure is substituted.
- A representative sequence, preferably with a structure link, is chosen from among those in the alignment.
- A consensus sequence is made.
- A position-specific scoring matrix (PSSM) is constructed.

The Conserved Domain search (CD-search) compares a protein sequence to the PSSMs in the CDD database to identify conserved domains within it and to identify a 3-D modeling template. Since the PSSMs are the "subject", instead of the query as in PSI-Blast, the CD-search is a form of Reverse Position-Specific Blast (RPS-Blast).

The Conserved Domain Architecture Retrieval Tool (CDART) can be used to identify proteins containing the domain(s) present in the query sequence. Conserved domain(s) present in all sequences within Entrez proteins are identified using CD-search during routine NCBI processing. These pre-computed results are accessed through CDART.

The Vector Alignment Search Tool (VAST) is a computer algorithm developed at NCBI to detect similar protein 3-dimensional structures. The "structure neighbors" for every structure in NCBI' Molecular Modeling Database (MMDB) are pre-computed. These neighbors can be used to identify distant homologs that cannot be recognized by sequence comparison alone. A VAST-search can be used for determining the structure neighbors for recently solved structures not yet in MMDB.

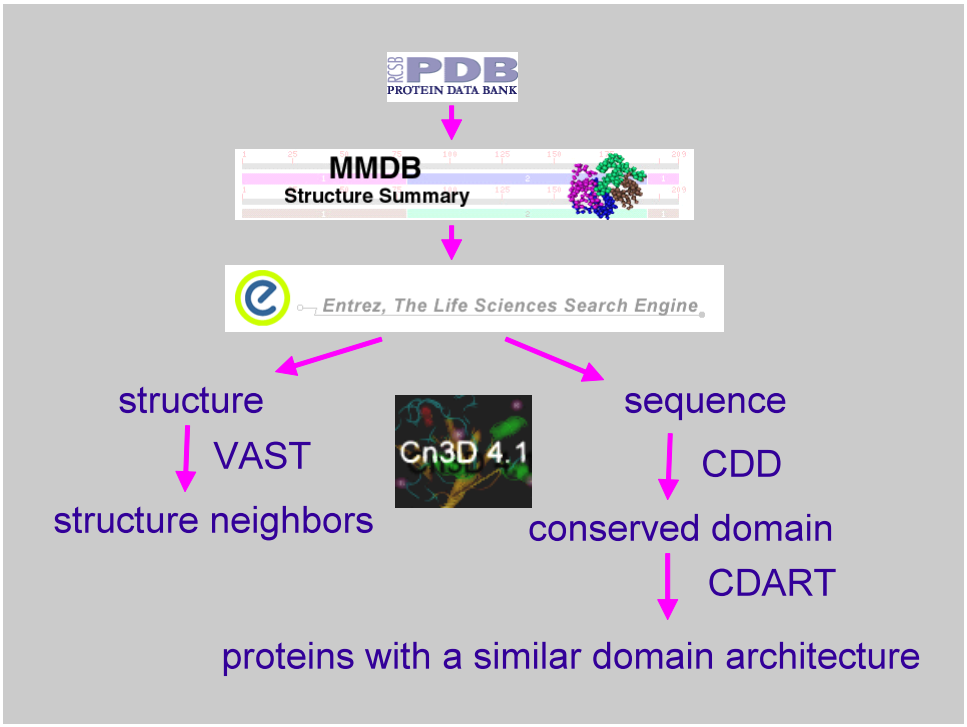
Cn3D is a helper application for web browsers to view 3-dimensional structures from NCBI's Entrez retrieval service. Cn3D runs on Windows, Macintosh, and Unix. Cn3D simultaneously displays structure, sequence, and alignment, and now has powerful annotation and alignment editing features.

In this exercise, we will learn to

- Identify a conserved domain present in the query protein using **CDD**
- Search for other proteins containing similar domain(s) using **CDART**
- Explore a 3D modeling template for the query sequence using **CDD**
- Find similar structures using **VAST**
- Visualize and annotate the 3D protein structures using **Cn3D**

The remainder of the handout includes the introductory slides and the screen shots of the exercise demonstrated in Problem 1.

Slides:



http://www.ncbi.nlm.nih.gov/Structure/cdd/cdd.shtml

Conserved Domain

- recurring unit in molecular evolution, whose extents can be determined by sequence and structure analysis
- performs a particular function
- represented as a multiple local sequence alignment of proteins containing the domain

NCBI

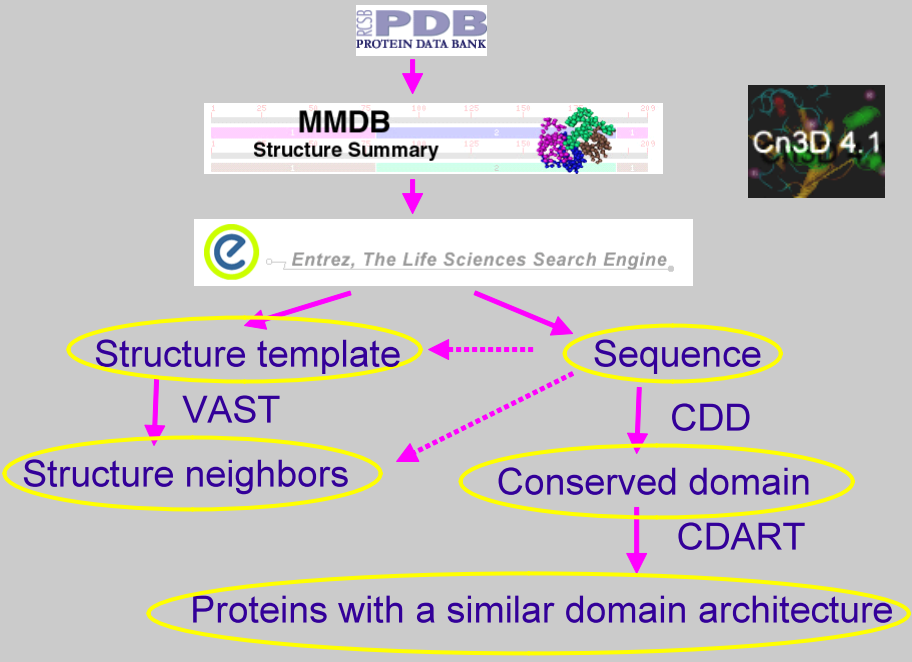
Conserved Domain Database

Pfam SMART COG KOG PRK

Curated CDs

- A position-specific scoring matrix (PSSM) is calculated
- CD-Search can be used to search against the PSSMs
- Manual curation of CDs has begun

NCBI



Exercise 1

In this problem, we will follow these steps:

A. Identify conserved domain(s) present in a protein.
B. Search for other proteins containing similar domain(s).
C. Explore a 3D modeling template for the query sequence.
D. Find distant sequence homologs that may not be identified by BLAST.

NCBI's Conserved Domain Search allows you to match your protein sequence to a library of conserved protein domains, generate a multiple sequence alignment based on this match, and explore 3D modeling templates for your sequence.

Navigate to the CDD Search page at:
http://www.ncbi.nlm.nih.gov/Structure/cdd/wrpsb.cgi

Paste the following protein sequence in the CD-Search query box and run the search.

MDPIALTAAVGADLLGDGRPETLWLGIGTLLMLIGTFYFIVKGWGVTDKEAREYY
SITILVPGIASAAYLSMFFGIGLTEVQVGSEMLDIYYARYADWLFTTPLLLLDLALL
AKVDRVSIGTLVGVDALMIVTGLVGALSHTPLARYTWWLFSTICMIVVLYFLATS
LRAAAKERGPEVASTFNTLTALVLVLWTAYPILWIIGTEGAGVVGLGIETLLFMVL
DVTAKVGFGFILLRSRAILGDTEAPEPSAGAEASAAD

A. What is the domain present in this protein?

Obtain more information about the bacteriorhodopsin domain by searching in NCBI's Bookshelf

http://www.ncbi.nlm.nih.gov/books/

B. Go back to the CD-Search results page. Obtain a list of proteins with similar domain architecture by clicking on the "Search for similar domain architectures" button. To display the records, click on the link to the sequences and from there on the “Look up Sequences in Entrez”. Change the display from “Summary” to “FASTA”.

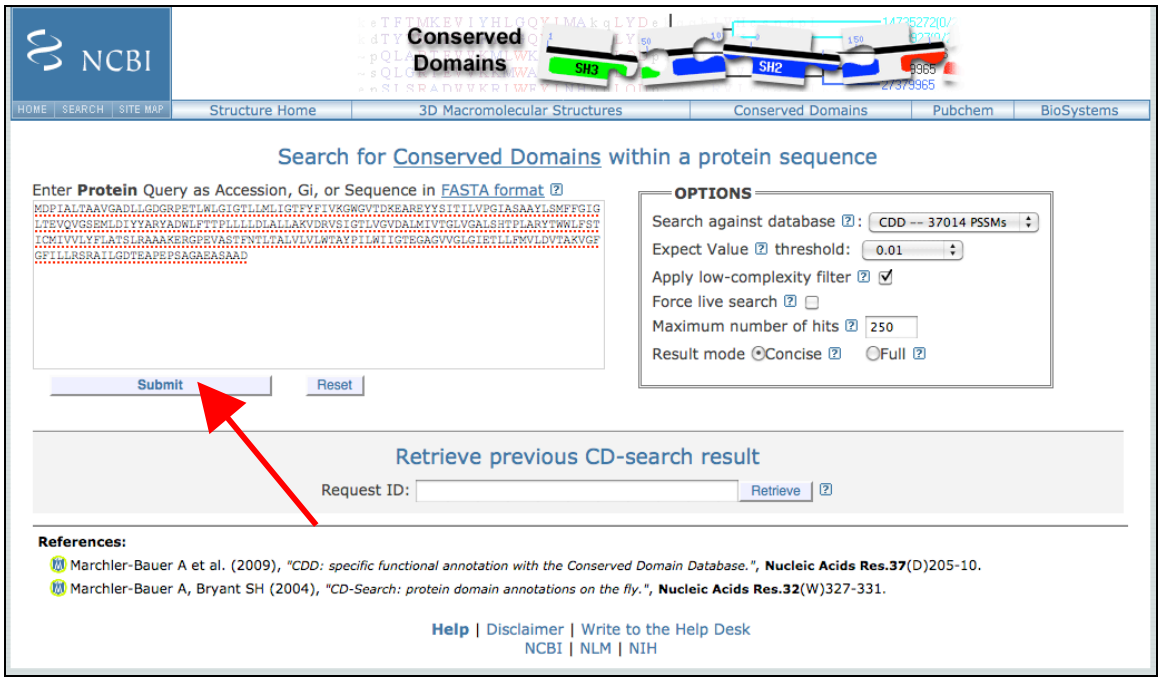
C. Go back to the CD-Search results page. Generate a multiple sequence alignment for the top 10 sequences representative of the conserved domain hit by clicking on the full display button, then the Pfam domain entry graphic of the domain. Use the "Row Display" list box pull down menu to specify "up to 5" sequences and reformat sequence alignment. Extend the “Structure” display and invoke Cn3D with a display of a 3D modeling template and a multiple sequence alignment including your query sequence by pressing the "Structure View" button.

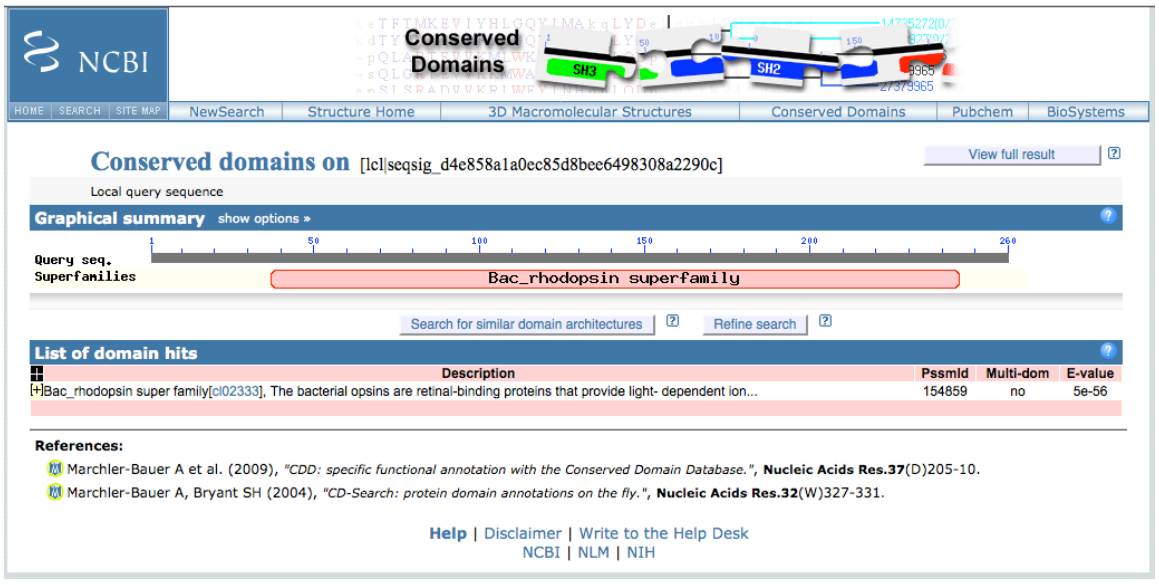
The structure of the *Halobacterium salinarum* bacteriorhodopsin mutant protein and its sequence alignment with our query protein are displayed. For a better view of the backbone, remove the side chains globally (Style--Edit global style--Protein side chains). The query protein contains a bacterial rhodopsin signature (FMVLDVTAKVGF) where K is the retinal binding site. Identify these residues in the query protein and highlight the corresponding lysine residue in the halorhodopsin protein sequence.

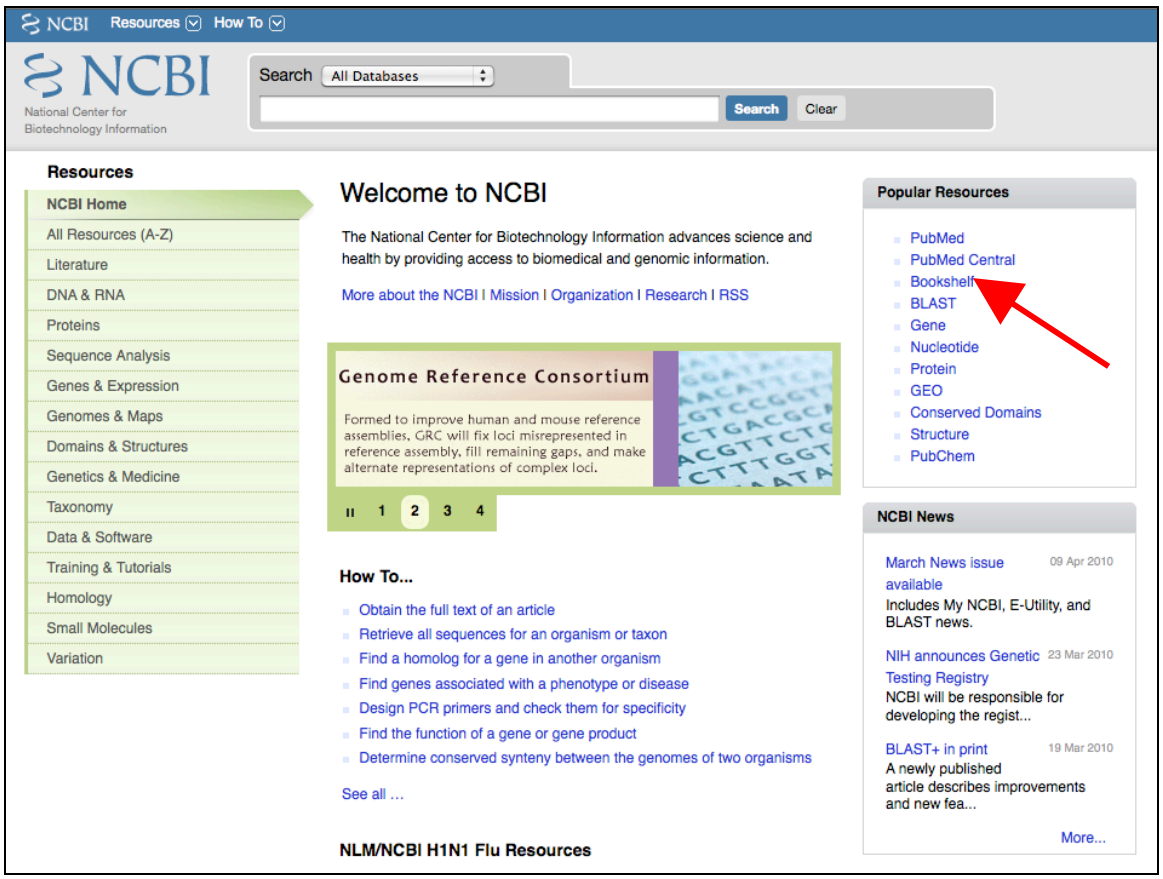
Display the side chains of this residue (Use Style--Annotate--New--Edit Style. Change the protein backbone Rendering to Tubes, Color Scheme to User Selection and User Color to choose the color for the highlighted residue, for example yellow. Repeat these steps for the Protein Side chains row and click the Protein Side chains on. Click on the “Done” button. To zoom in, press z on the keyboard. Identify the cofactor near the lysine residue.

D. To obtain the structural neighbors for the halorhodopsin protein, first click on the structure entry link, 2JAF, on the CD-Browser page. Then click Links → Structure on the bottom right, then on 2JAF again in the Entrez Structure page, and finally on the grey “Sequence A” graphic. You will see a graphical representation of the regions aligned by VAST. To view the statistics in tabular format, select Table from the “in” portion of the List menu line and click list. Select one or more of the check boxes next to the structure neighbors and view by clicking on the "View 3D Structure" button.

Screen images:



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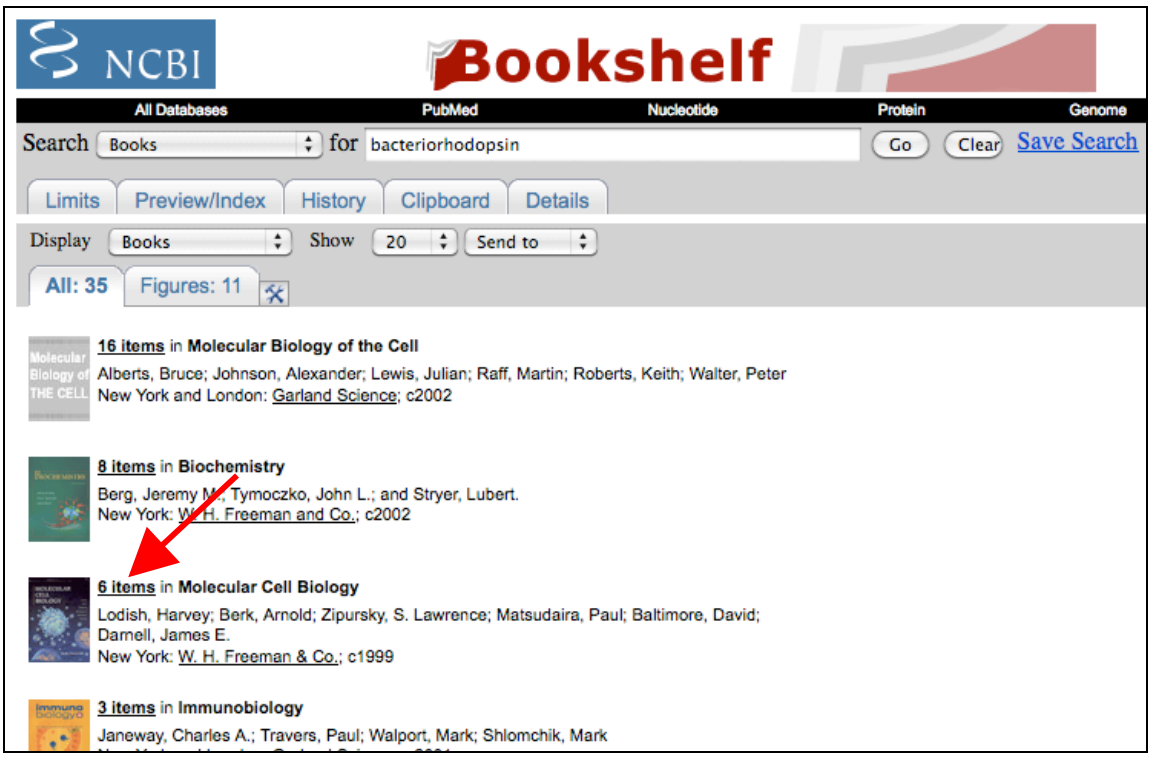
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6 items in Molecular Cell Biology
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New York: W. H. Freeman & Co.; c1999
3 items in Immunobiology
Janeway, Charles A.; Travers, Paul; Walport, Mark; Shlomchik, Mark

Many Integral Proteins Contain Multiple Transmembrane α Helices

Although Figure 3-33 depicts glycophorin as a monomer with a single α helix spanning the bilayer, this protein is present in erythrocyte membranes as a dimer of two identical polypeptide chains. The two membrane-spanning α helices of glycophorin are thought to form a coiled-coil structure (see Figure 3-9a) stabilized by specific interactions between the amino acid side chains at the interface of the two helices. It is now known that many other transmembrane proteins contain two or more membrane-spanning α helices. For instance, the *bacterial photosynthetic reaction center (PRC)* comprises four subunits and several prosthetic groups, including four chlorophyll molecules. In this complex protein, three of the four subunits span the membrane; two of these subunits (L and M) each contain five membrane-spanning α helices (see Figure 16-40).

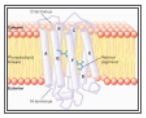

Figure 3-34
Overall structure of bacteriorhodopsin as deduced from (more...)

A large and important family of integral proteins is defined by the presence of seven membrane-spanning α helices. More than 150 such "seven-spanning" membrane proteins have been identified. This class of integral proteins is typified by *bacteriorhodopsin,* a protein found in a photosynthetic bacterium (Figure 3-34). Absorption of light by the retinal group attached to bacteriorhodopsin causes a conformational change in the protein that results in pumping of protons from the cytosol across the bacterial membrane to the extracellular space. The proton concentration gradient thus generated across the membrane is used to synthesize ATP, as discussed in Chapter 16. Both the overall arrangement of the seven α helices in bacteriorhodopsin and the identity of most of the amino acids can be resolved by computer analysis of micrographs of two-dimensional crystals of the membrane-embedded protein taken at various angles to the electron beam.

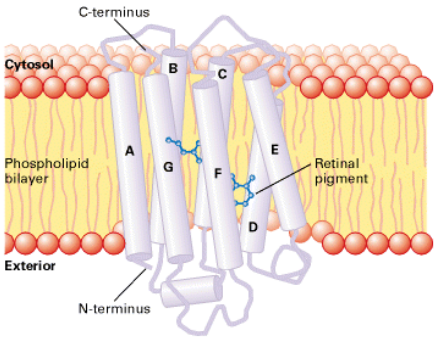

Figure 3-34. Overall structure of bacteriorhodopsin as deduced from electron diffraction analyses of two-dimensional crystals of the protein in the bacterial membrane. The seven membrane-spanning α helices are labeled A–G. The retinal pigment is covalently attached to lysine 216 in helix G. The approximate position of the protein in the phospholipid bilayer is indicated. [Adapted from R. Henderson et al., 1990, *J. Mol. Biol.* **213**:899.

Navigation
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3.2. Folding, Modification, and Degradation of Proteins
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3.4. Membrane Proteins
3.5. Purifying, Detecting, and Characterizing Proteins
PERSPECTIVES for the Future
PERSPECTIVES in the Literature
Testing Yourself on the Concepts
MCAT/GRE-Style Questions
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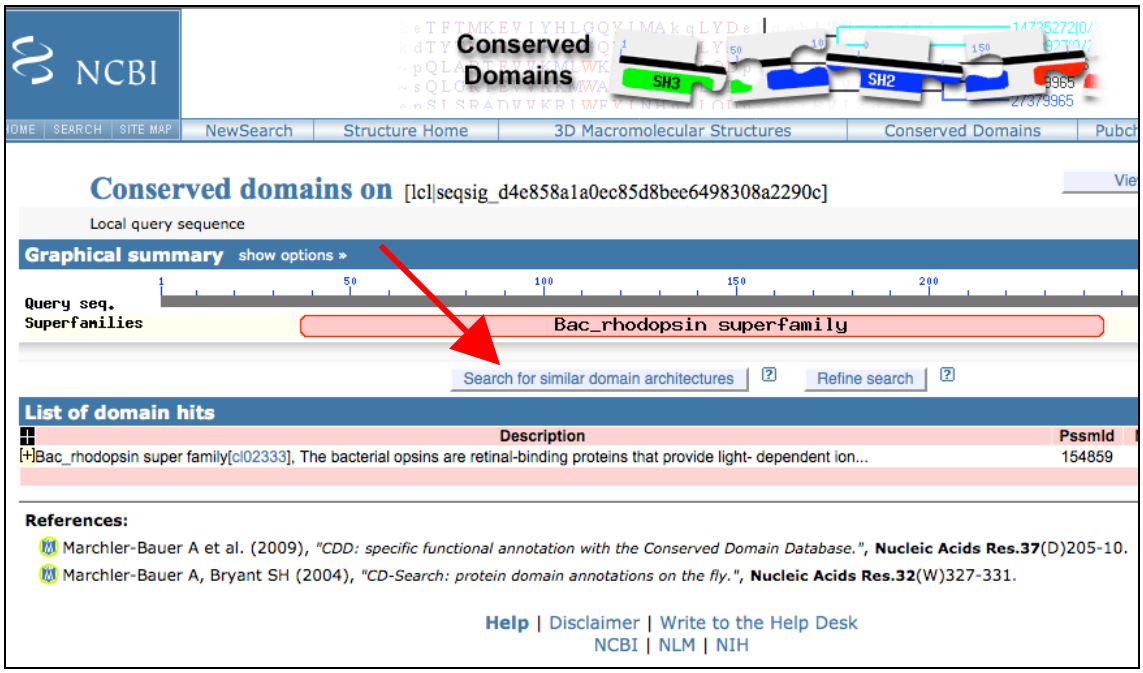
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References:
Marchler-Bauer A et al. (2009), "CDD: specific functional annotation with the Conserved Domain Database.", Nucleic Acids Res.37(D)205-10.
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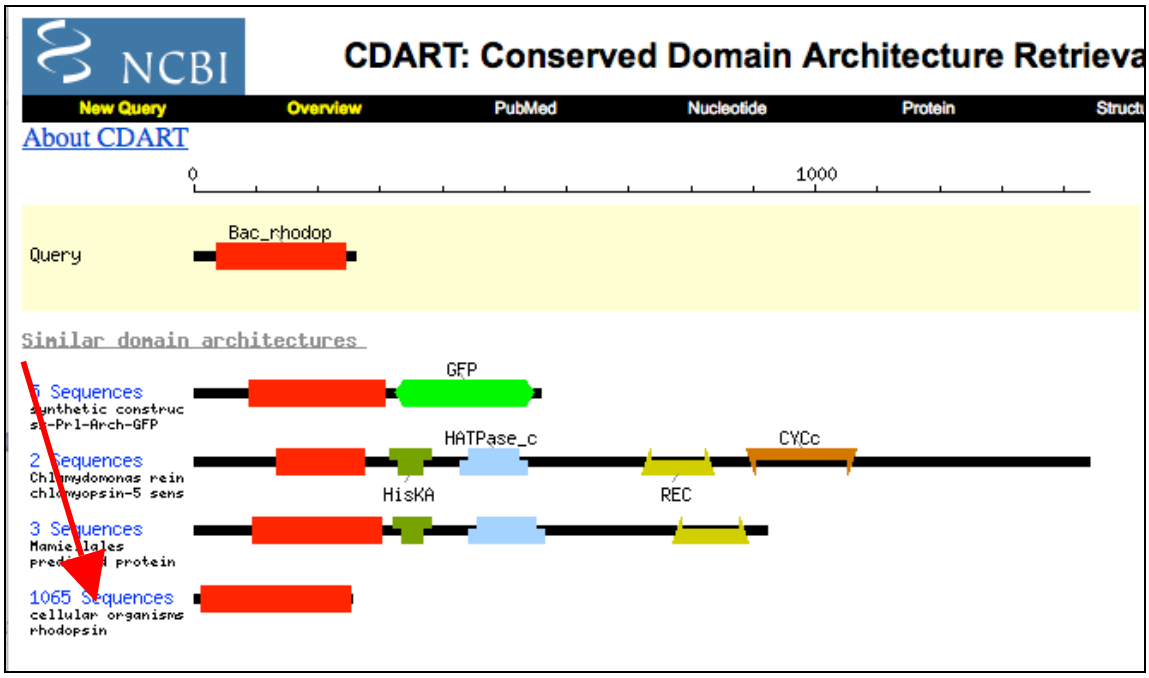
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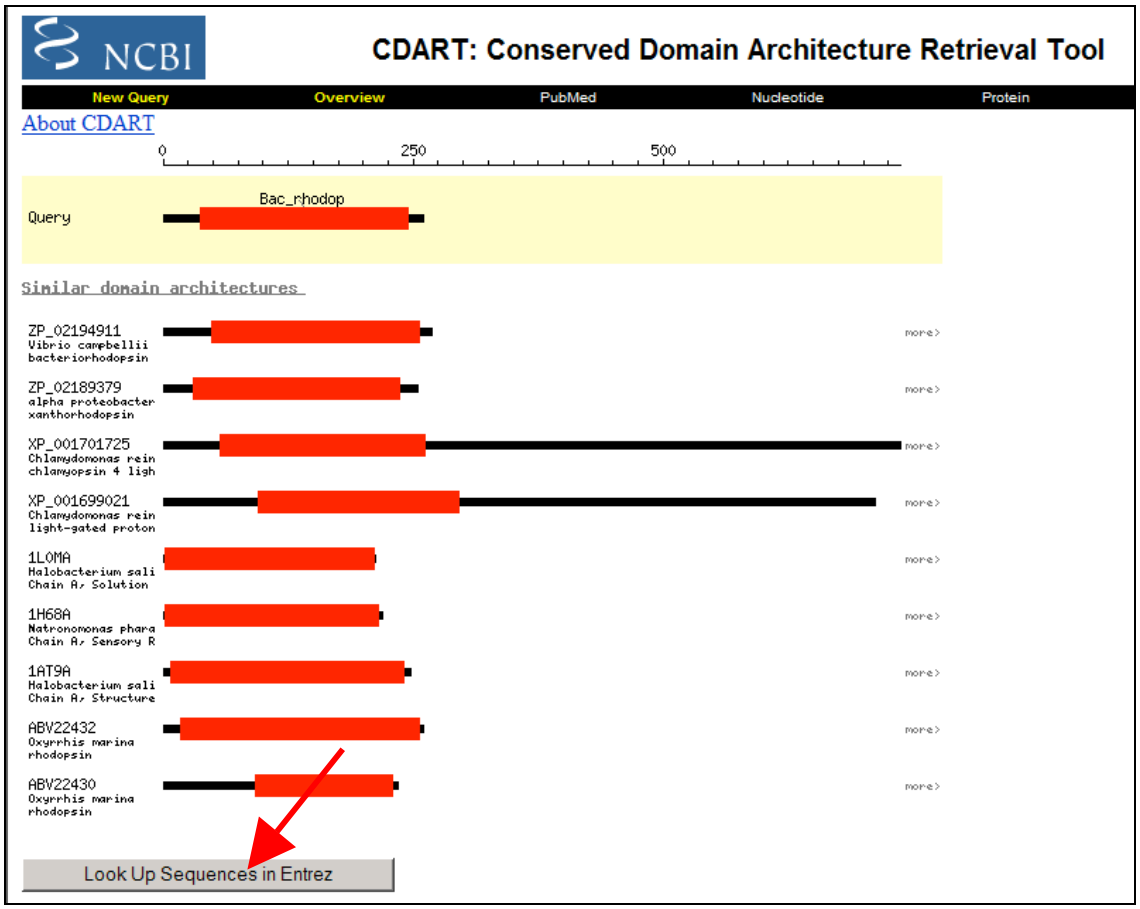
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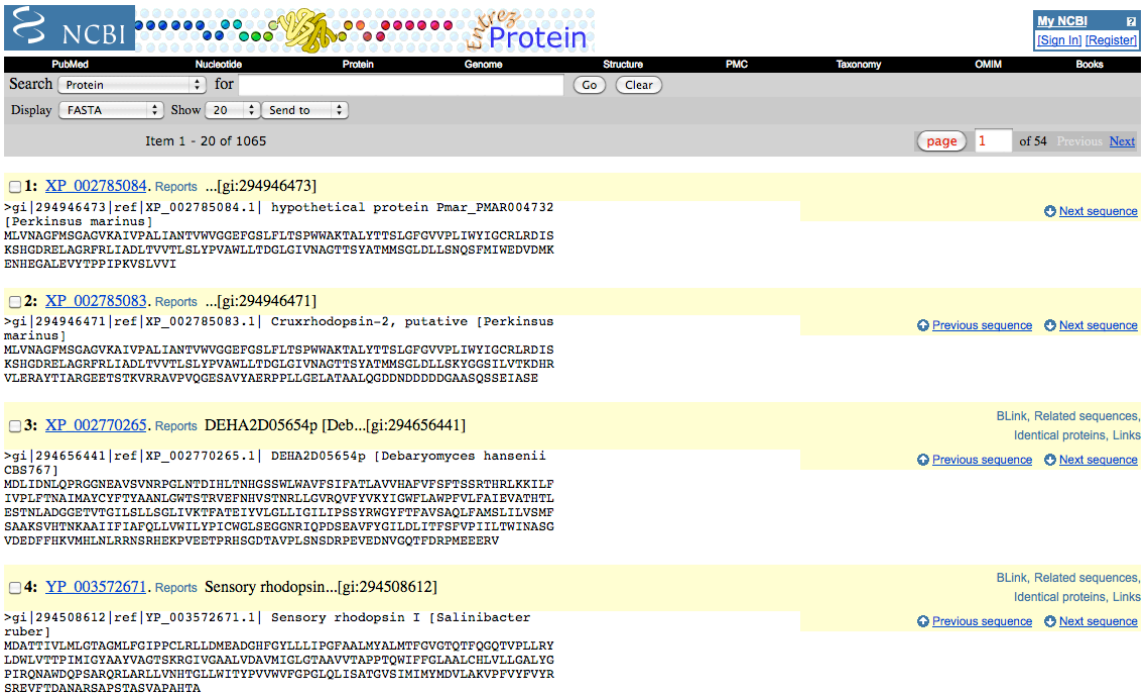
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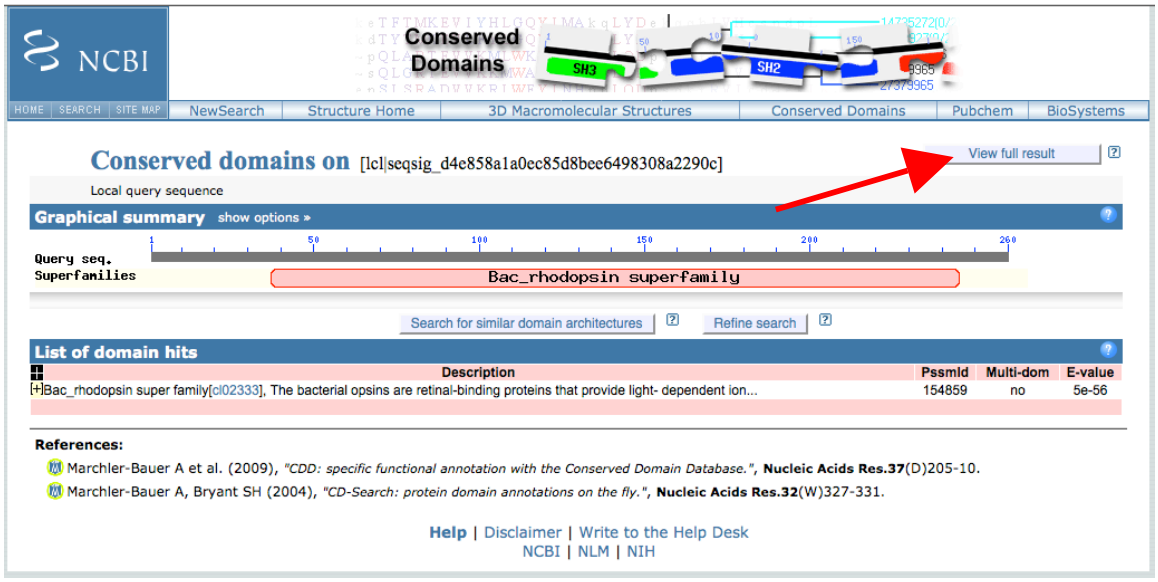
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Superfamilies
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References:
Marchler-Bauer A et al. (2009), "CDD: specific functional annotation with the Conserved Domain Database.", Nucleic Acids Res.37(D)205-10.
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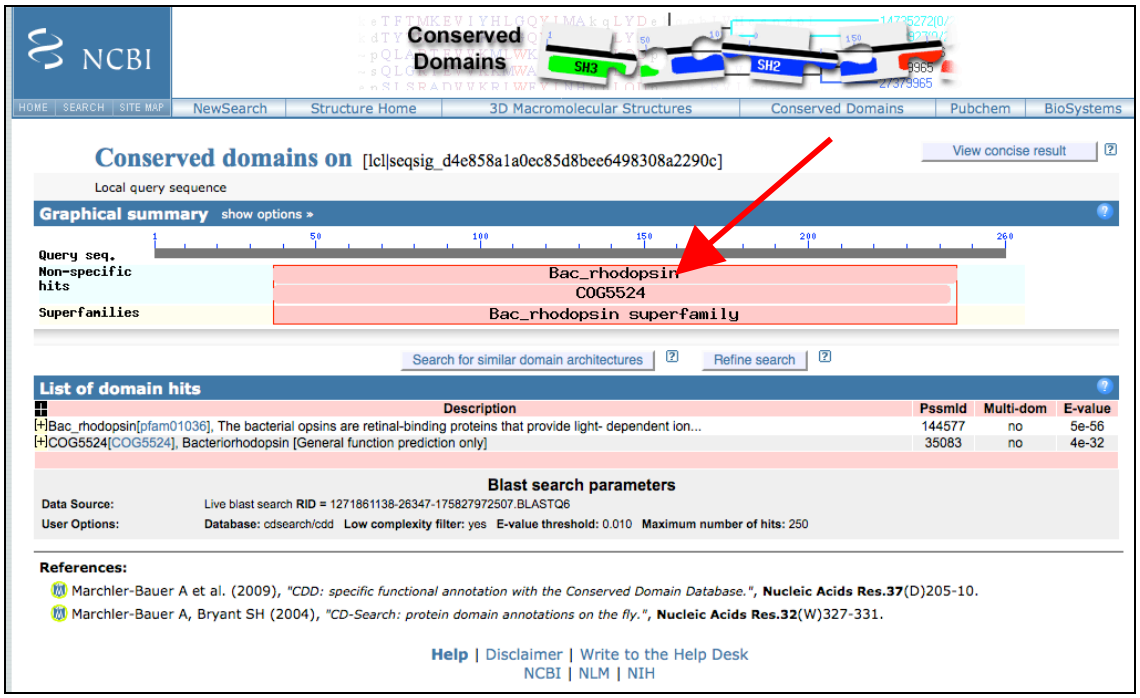
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Bac_rhodopsin superfamily
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Refine search
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Marchler-Bauer A et al. (2009), "CDD: specific functional annotation with the Conserved Domain Database.", Nucleic Acids Res.37(D)205-10.
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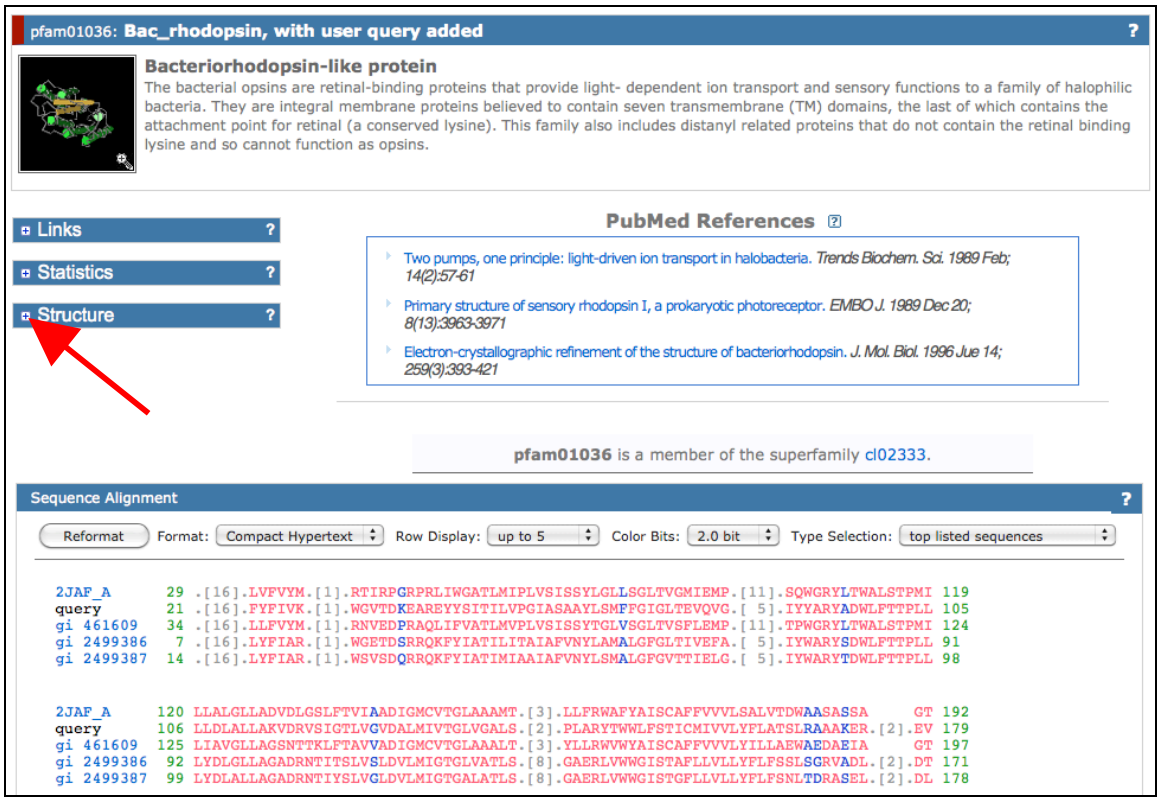
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Bacteriorhodopsin-like protein
The bacterial opsins are retinal-binding proteins that provide light- dependent ion transport and sensory functions to a family of halophilic bacteria. They are integral membrane proteins believed to contain seven transmembrane (TM) domains, the last of which contains the attachment point for retinal (a conserved lysine). This family also includes distanyl related proteins that do not contain the retinal binding lysine and so cannot function as opsins.
Links
Statistics
Structure
PubMed References
Two pumps, one principle: light-driven ion transport in halobacteria. Trends Biochem. Sci. 1989 Feb; 14(2):57-61
Primary structure of sensory rhodopsin I, a prokaryotic photoreceptor. EMBO J. 1989 Dec 20; 8(13):3963-3971
Electron-crystallographic refinement of the structure of bacteriorhodopsin. J. Mol. Biol. 1996 Jue 14; 259(3):393-421
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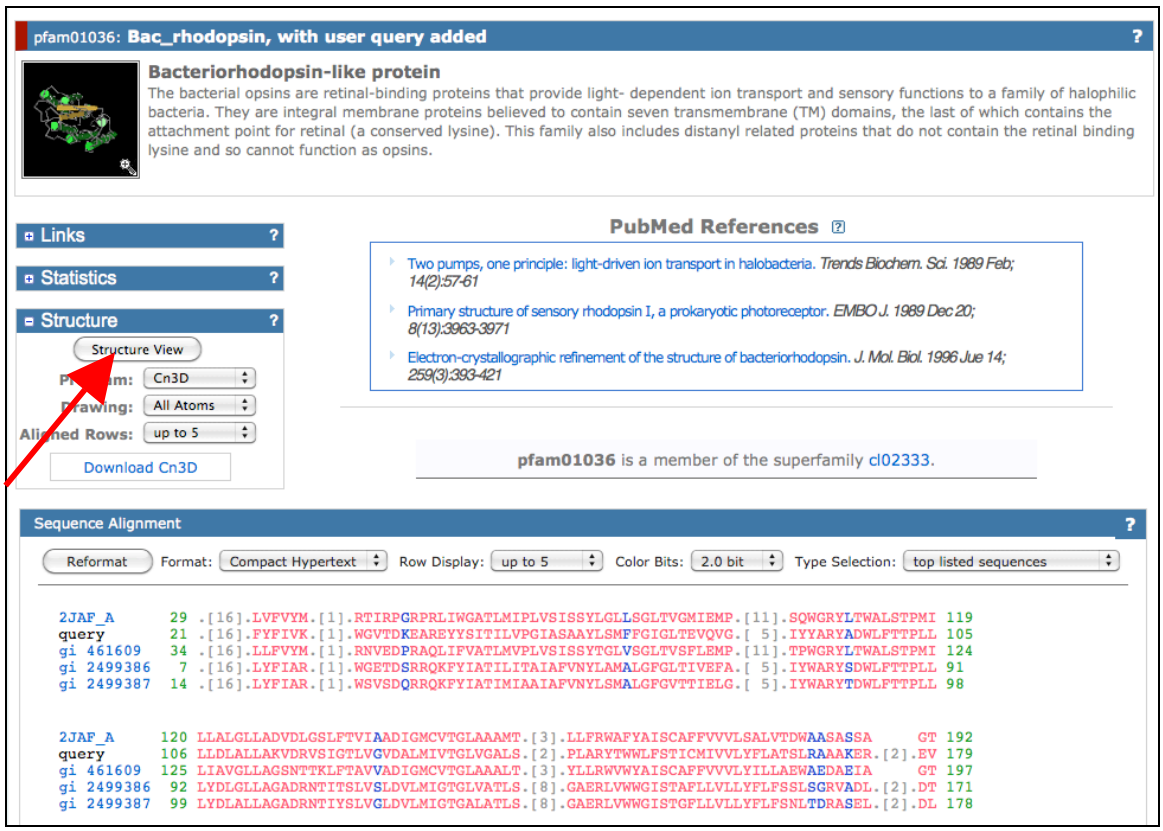
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Bacteriorhodopsin-like protein
The bacterial opsins are retinal-binding proteins that provide light- dependent ion transport and sensory functions to a family of halophilic bacteria. They are integral membrane proteins believed to contain seven transmembrane (TM) domains, the last of which contains the attachment point for retinal (a conserved lysine). This family also includes distanyl related proteins that do not contain the retinal binding lysine and so cannot function as opsins.
Links
Statistics
Structure
Structure View
Cn3D
All Atoms
up to 5
Download Cn3D
PubMed References
Two pumps, one principle: light-driven ion transport in halobacteria. Trends Biochem. Sci. 1989 Feb; 14(2):57-61
Primary structure of sensory rhodopsin I, a prokaryotic photoreceptor. EMBO J. 1989 Dec 20; 8(13):3963-3971
Electron-crystallographic refinement of the structure of bacteriorhodopsin. J. Mol. Biol. 1996 Jue 14; 259(3):393-421
pfam01036 is a member of the superfamily cl02333.
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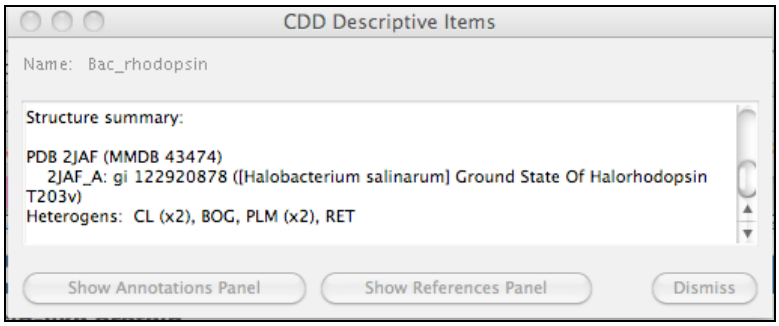
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Show Annotations Panel
Show References Panel
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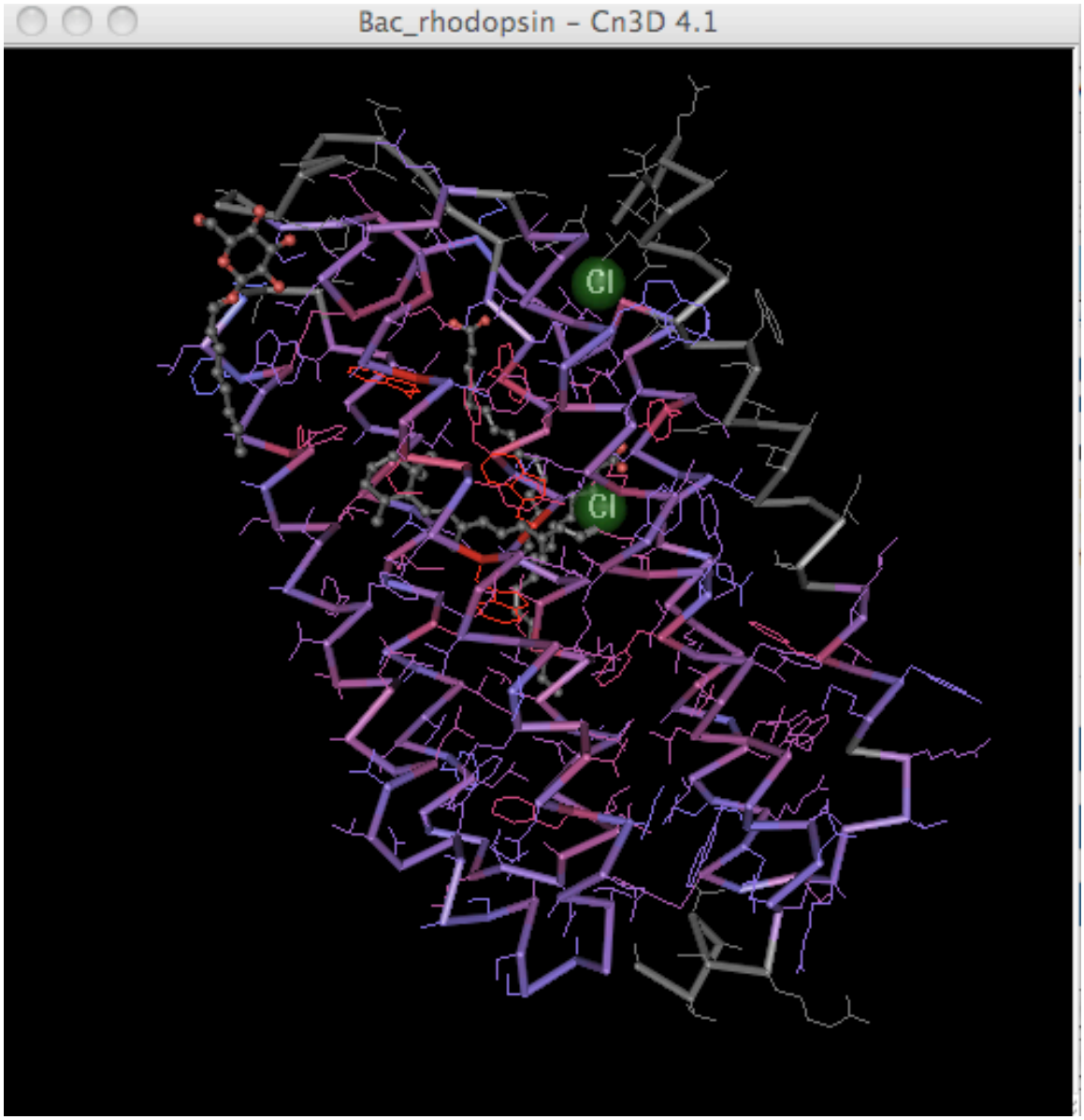
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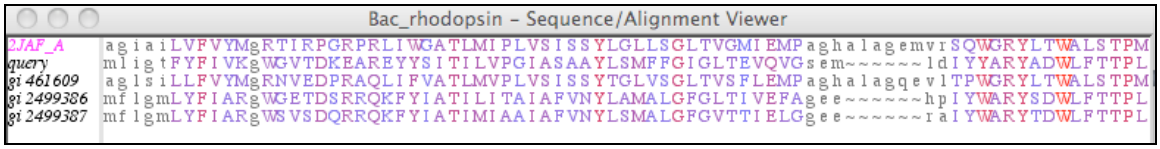
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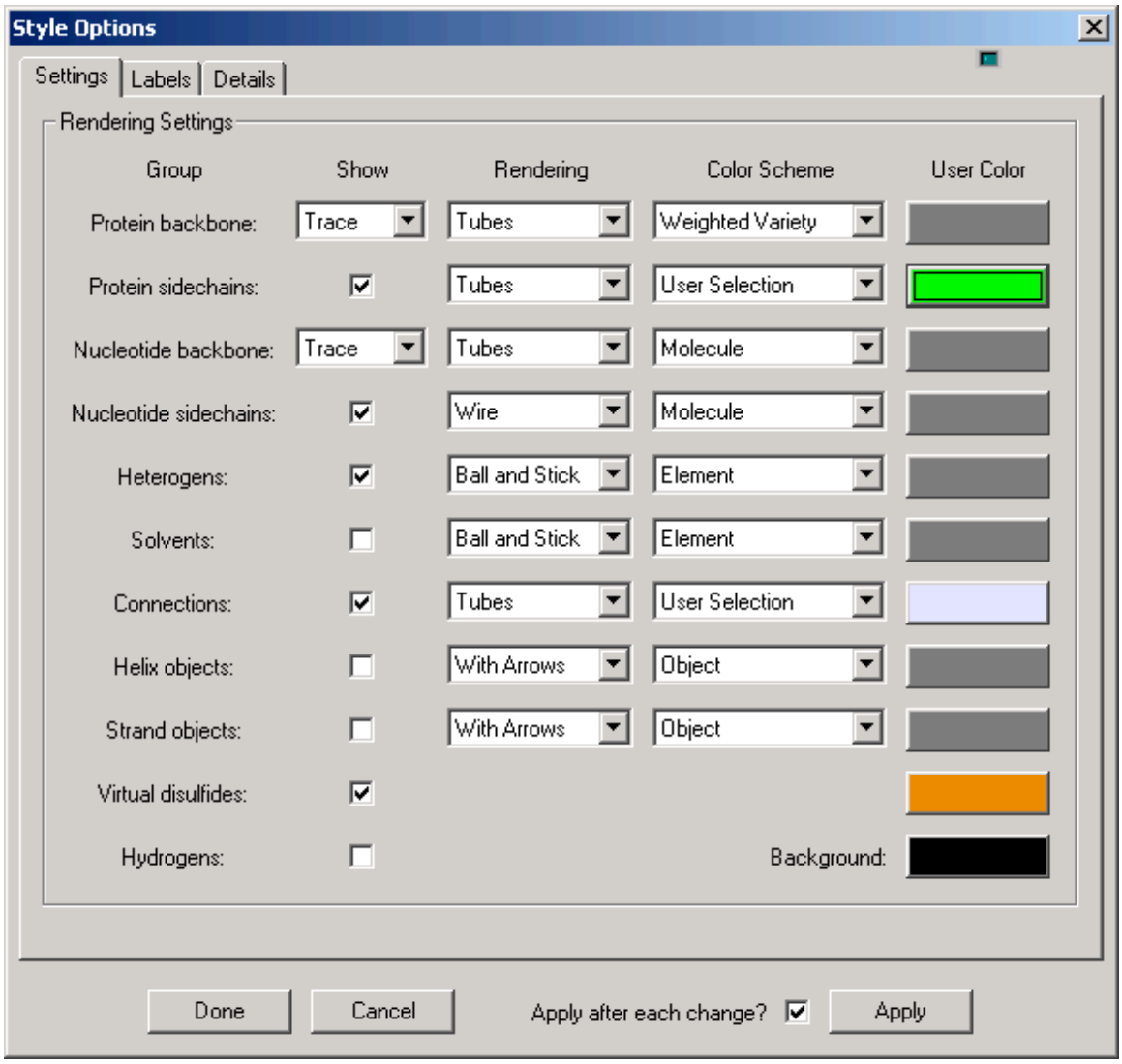
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Solvents:
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Tubes
User Selection
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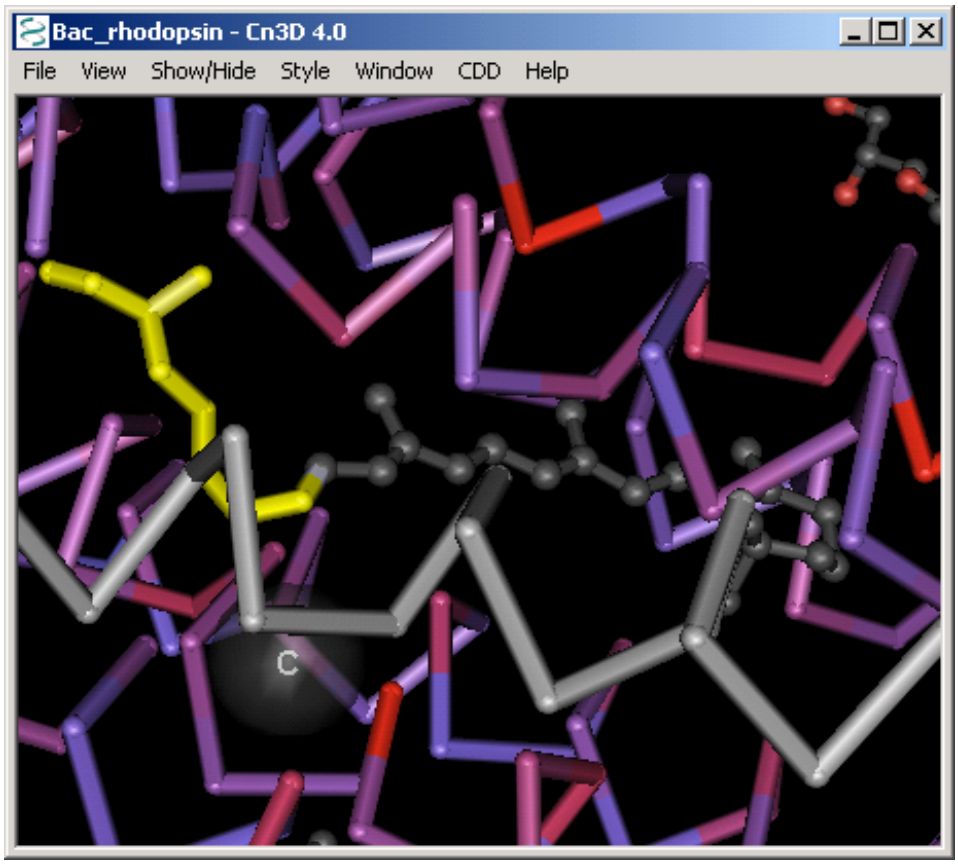
Bac_rhodopsin - Cn3D 4.0
File View Show/Hide Style Window CDD Help
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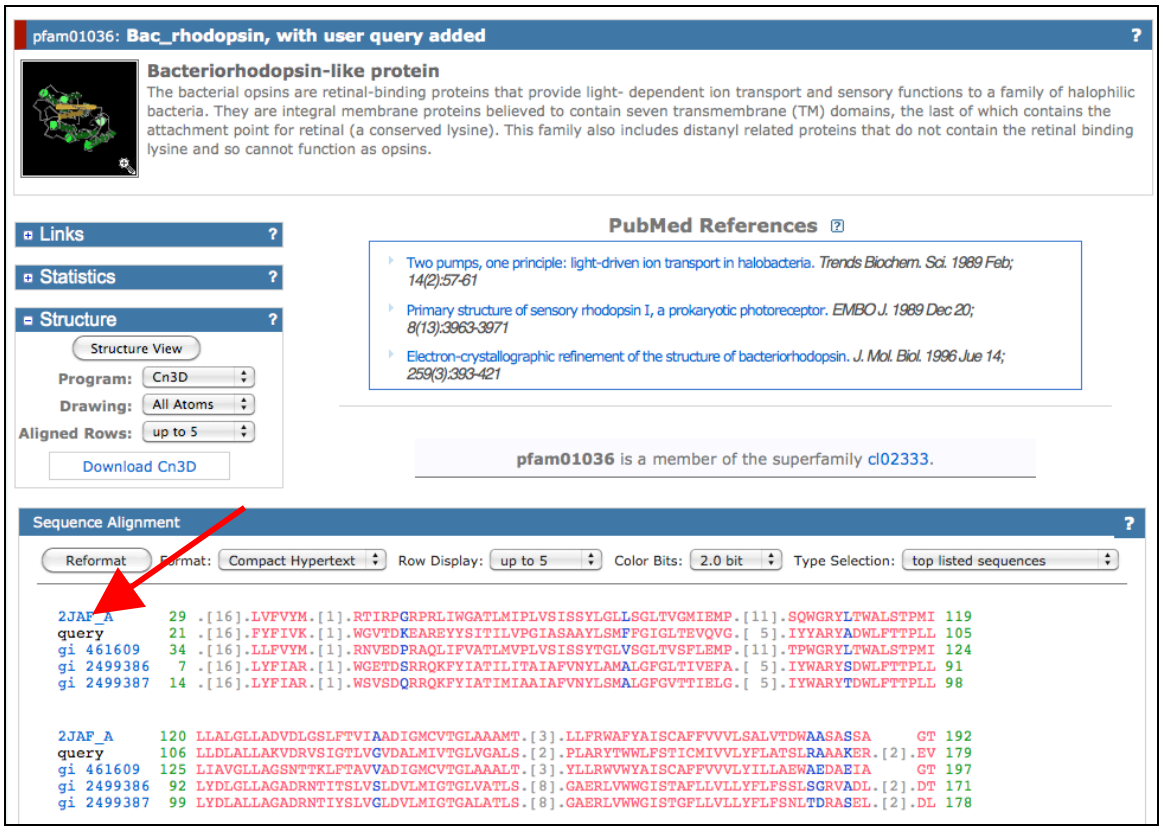
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Bacteriorhodopsin-like protein
The bacterial opsins are retinal-binding proteins that provide light- dependent ion transport and sensory functions to a family of halophilic bacteria. They are integral membrane proteins believed to contain seven transmembrane (TM) domains, the last of which contains the attachment point for retinal (a conserved lysine). This family also includes distanyl related proteins that do not contain the retinal binding lysine and so cannot function as opsins.
Links
Statistics
Structure
Structure View
Program: Cn3D
Drawing: All Atoms
Aligned Rows: up to 5
Download Cn3D
PubMed References
Two pumps, one principle: light-driven ion transport in halobacteria. Trends Biochem. Sci. 1989 Feb; 14(2):57-61
Primary structure of sensory rhodopsin I, a prokaryotic photoreceptor. EMBO J. 1989 Dec 20; 8(13):3963-3971
Electron-crystallographic refinement of the structure of bacteriorhodopsin. J. Mol. Biol. 1996 Jue 14; 259(3):393-421
pfam01036 is a member of the superfamily cl02333.
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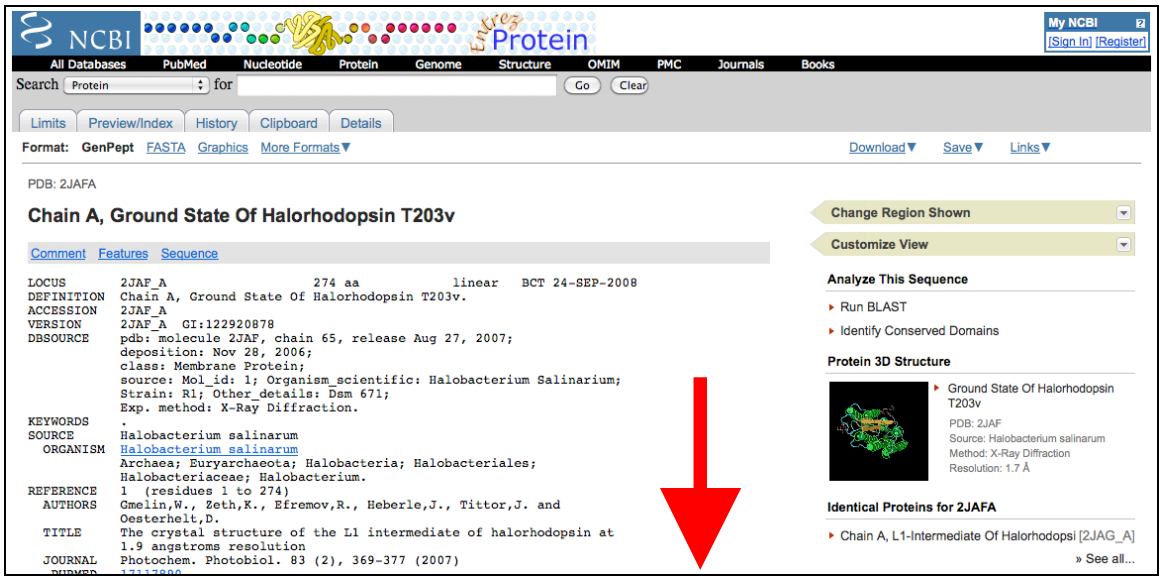
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Format: GenPept FASTA Graphics More Formats▼
Download▼ Save▼ Links▼
PDB: 2JAFA
Chain A, Ground State Of Halorhodopsin T203v
Comment Features Sequence
LOCUS 2JAF_A 274 aa linear BCT 24-SEP-2008
DEFINITION Chain A, Ground State Of Halorhodopsin T203v.
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1.9 angstroms resolution
JOURNAL Photochem. Photobiol. 83 (2), 369-377 (2007)
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Customize View
Analyze This Sequence
Run BLAST
Identify Conserved Domains
Protein 3D Structure
Ground State Of Halorhodopsin T203v
PDB: 2JAF
Source: Halobacterium salinarum
Method: X-Ray Diffraction
Resolution: 1.7 Å
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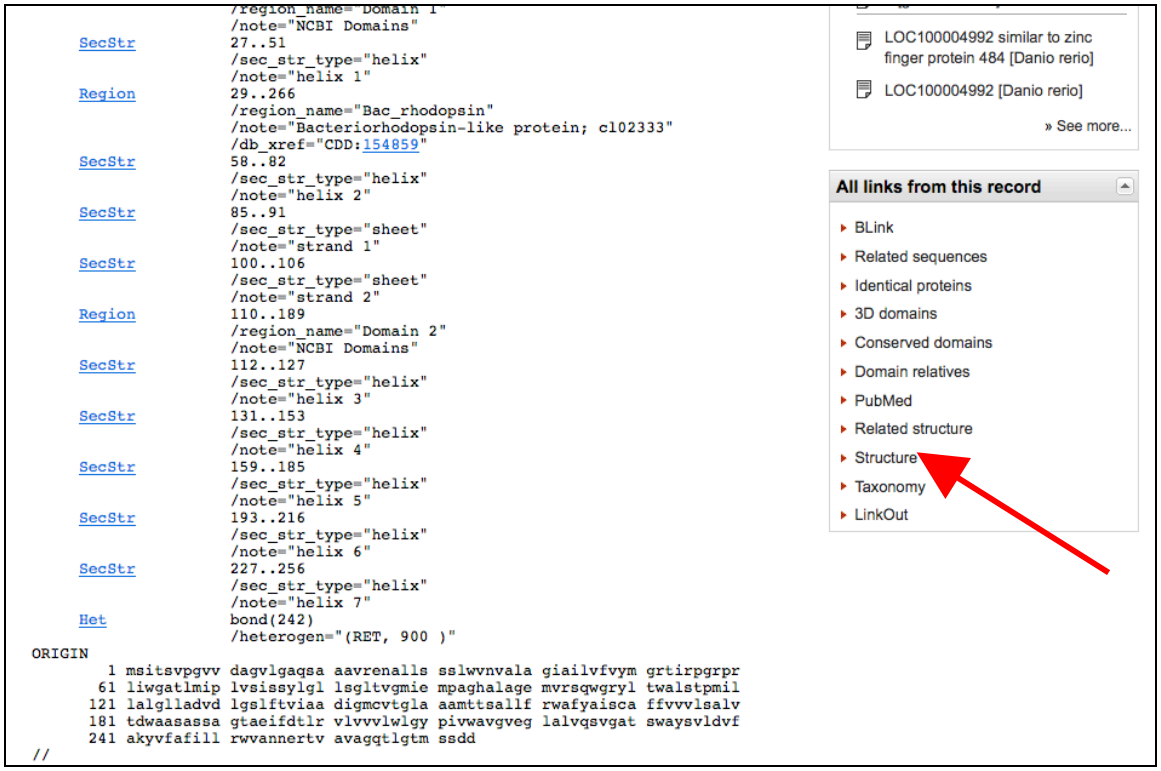
Chain A, L1-Intermediate Of Halorhodopsi [2JAG_A]
» See all...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//
LOC100004992 similar to zinc finger protein 484 [Danio rerio]
LOC100004992 [Danio rerio]
» See more...
All links from this record
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Related sequences
Identical proteins
3D domains
Conserved domains
Domain relatives
PubMed
Related structure
Structure
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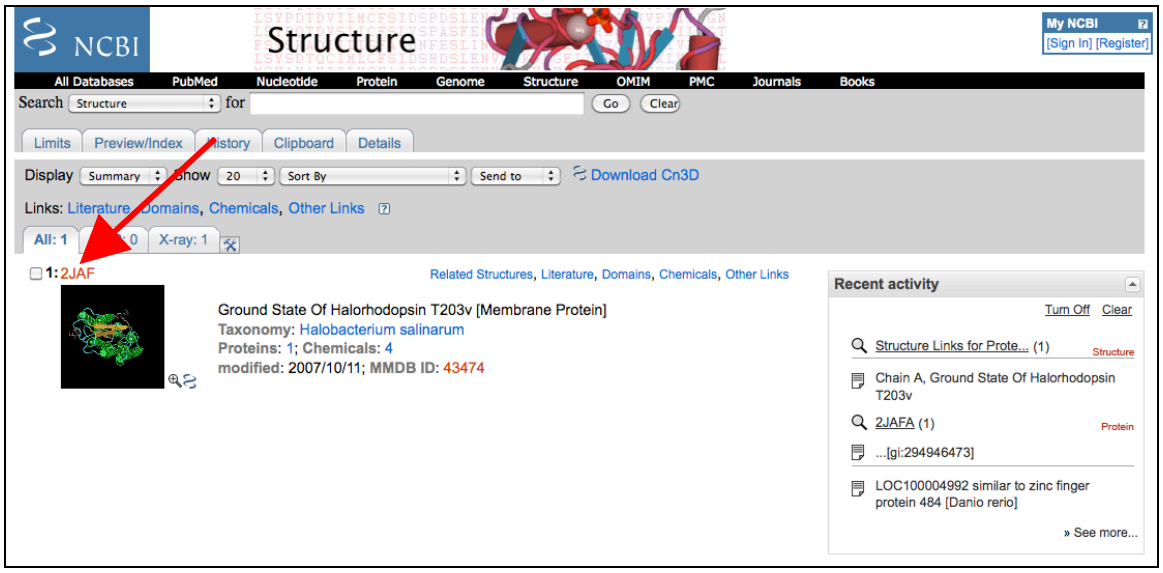
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Links: Literature, Domains, Chemicals, Other Links
All: 1 X-ray: 1
1: 2JAF
Related Structures, Literature, Domains, Chemicals, Other Links
Ground State Of Halorhodopsin T203v [Membrane Protein]
Taxonomy: Halobacterium salinarum
Proteins: 1; Chemicals: 4
modified: 2007/10/11; MMDB ID: 43474
Recent activity
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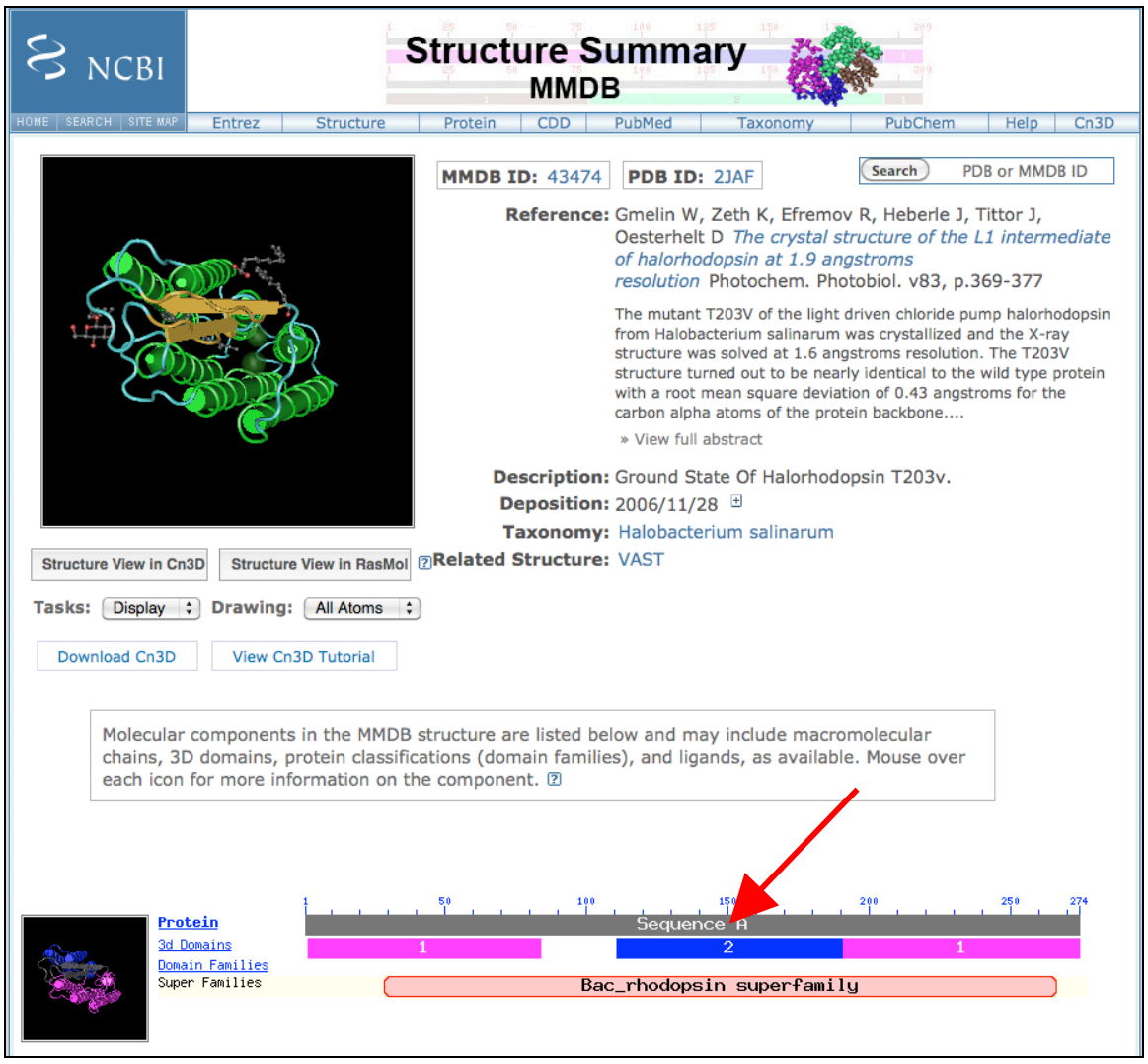
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Structure Summary
MMDB
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PDB ID: 2JAF
Search PDB or MMDB ID
Reference: Gmelin W, Zeth K, Efremov R, Heberle J, Tittor J, Oesterhelt D The crystal structure of the L1 intermediate of halorhodopsin at 1.9 angstroms resolution Photochem. Photobiol. v83, p.369-377
The mutant T203V of the light driven chloride pump halorhodopsin from Halobacterium salinarum was crystallized and the X-ray structure was solved at 1.6 angstroms resolution. The T203V structure turned out to be nearly identical to the wild type protein with a root mean square deviation of 0.43 angstroms for the carbon alpha atoms of the protein backbone....
» View full abstract
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Deposition: 2006/11/28
Taxonomy: Halobacterium salinarum
Related Structure: VAST
Structure View in Cn3D
Structure View in RasMol
Tasks: Display Drawing: All Atoms
Download Cn3D
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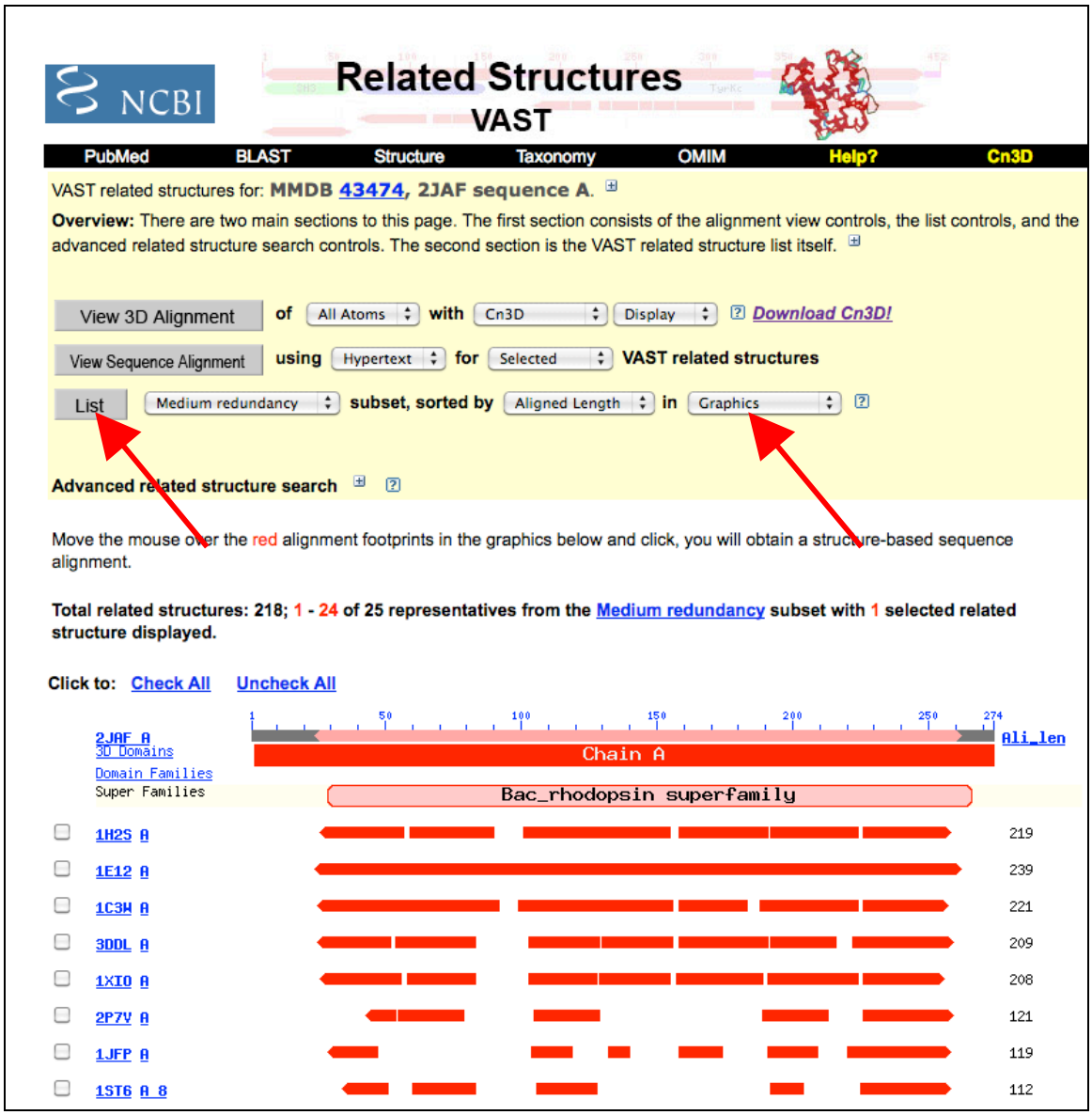
Molecular components in the MMDB structure are listed below and may include macromolecular chains, 3D domains, protein classifications (domain families), and ligands, as available. Mouse over each icon for more information on the component.
Protein
3d Domains
Domain Families
Super Families
Sequence A
1
2
1
Bac_rhodopsin superfamily


NCBI
Related Structures
VAST
PubMed BLAST Structure Taxonomy OMIM Help? Cn3D
VAST related structures for: MMDB 43474, 2JAF sequence A.
Overview: There are two main sections to this page. The first section consists of the alignment view controls, the list controls, and the advanced related structure search controls. The second section is the VAST related structure list itself.
View 3D Alignment of All Atoms with Cn3D Display Download Cn3D!
View Sequence Alignment using Hypertext for Selected VAST related structures
List Medium redundancy subset, sorted by Aligned Length in Graphics
Advanced related structure search
Move the mouse over the red alignment footprints in the graphics below and click, you will obtain a structure-based sequence alignment.
Total related structures: 218; 1 - 24 of 25 representatives from the Medium redundancy subset with 1 selected related structure displayed.
Click to: Check All Uncheck All
2JAF A
3D Domains
Domain Families
Super Families
Chain A
Bac_rhodopsin superfamily
Ali_len
1H2S A 219
1E12 A 239
1C3W A 221
3DDL A 209
1XIO A 208
2P7V A 121
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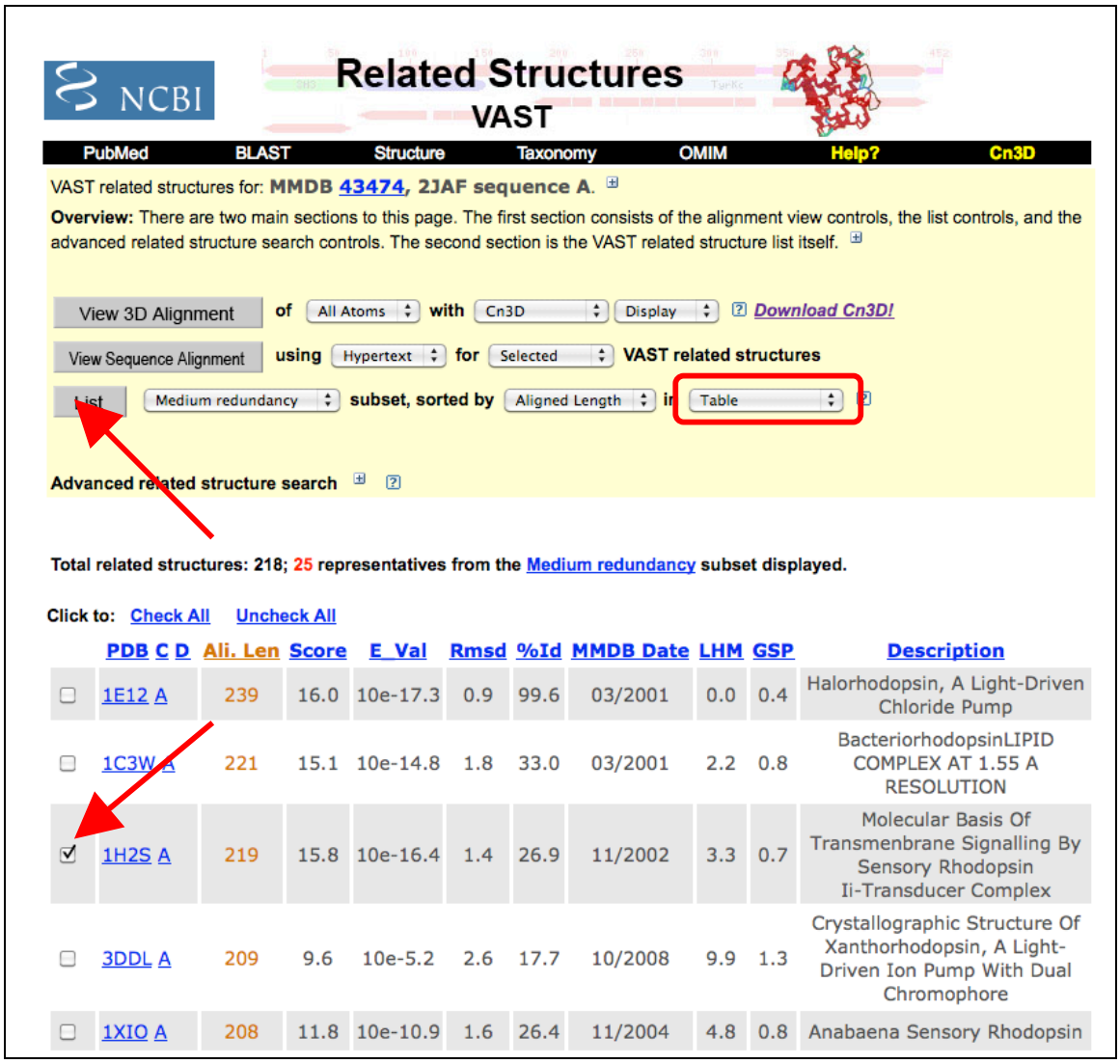
1ST6 A 8 112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VAST
PubMed
BLAST
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Taxonomy
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Help?
Cn3D
VAST related structures for: MMDB 43474, 2JAF sequence A.
Overview: There are two main sections to this page. The first section consists of the alignment view controls, the list controls, and the advanced related structure search controls. The second section is the VAST related structure list itself.
View 3D Alignment
of
All Atoms
with
Cn3D
Display
Download Cn3D!
View Sequence Alignment
using
Hypertext
for
Selected
VAST related structures
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Medium redundancy
subset, sorted by
Aligned Length
in
Table
Advanced related structure search
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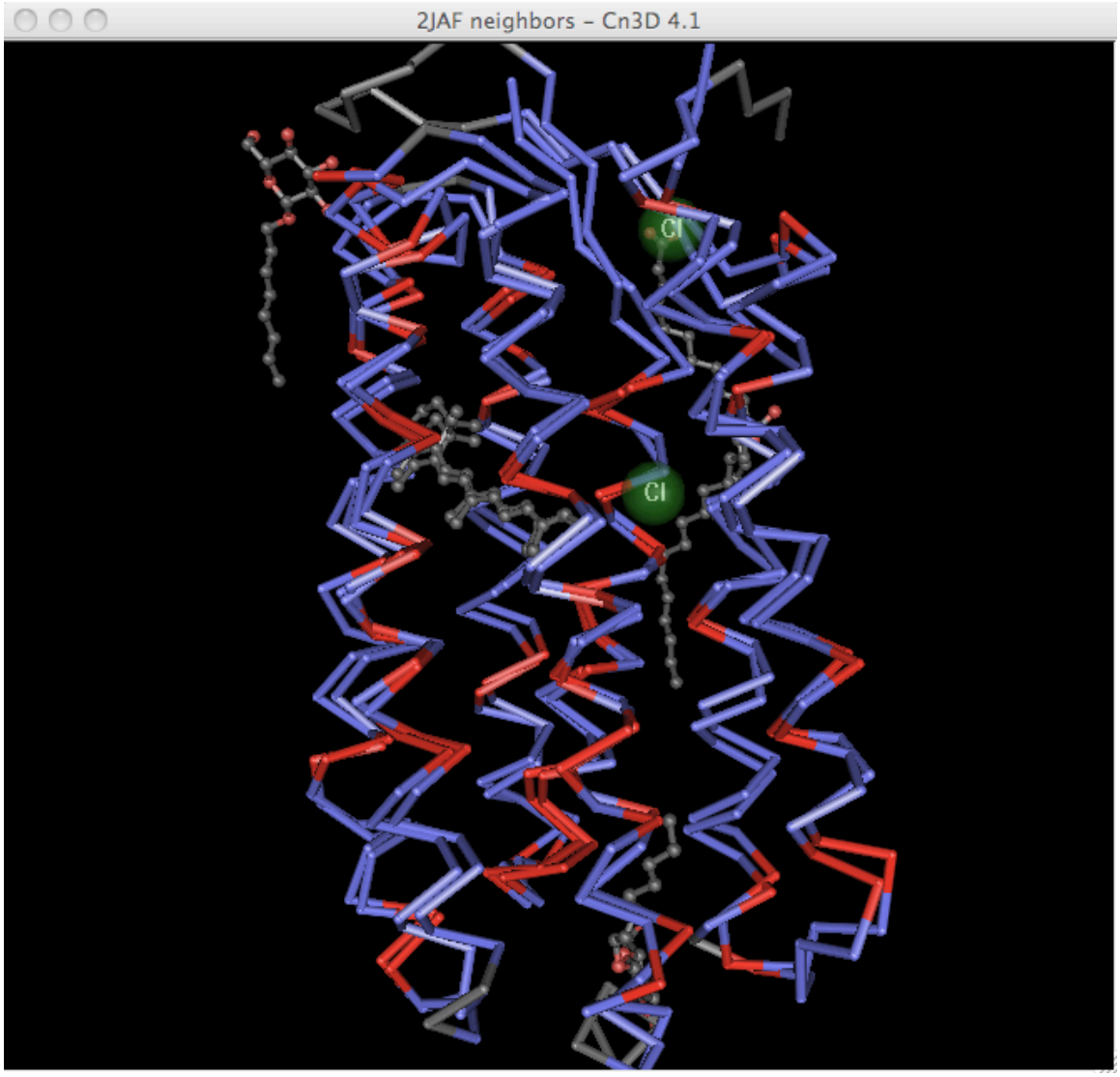
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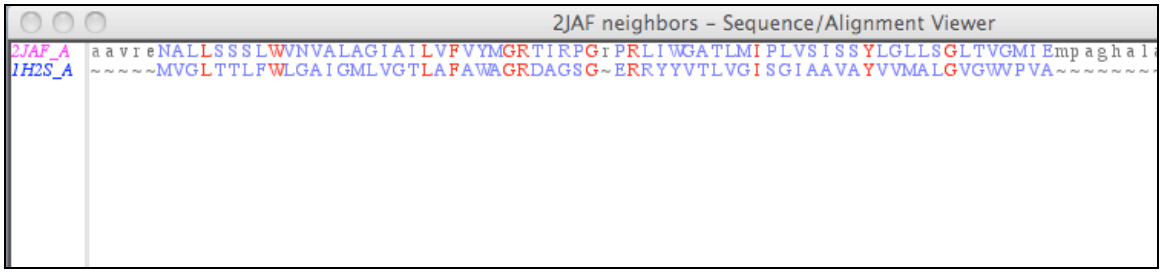
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Problem 2

In this problem, we will follow these steps:

A. Identify conserved domain(s) present in a protein.
B. Search for other proteins containing similar domain(s).
C. Explore a 3D modeling template for the query sequence.
D. Find distant sequence homologs that may not be identified by BLAST.

NCBI's Conserved Domain Search allows you to match your protein sequence to a library of conserved protein domains, generate a multiple sequence alignment based on this match, and explore 3D modeling templates for your sequence. Click on the CDD link provided below,

CDD

Paste the following protein sequence in the CD-Search query box and run the search.

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IESFIQGCCKDEWIKAAMTLTNVSEYVSSMGFNLELCKIAFCKSCAASGSLTLDQ
IEVICKDEAEVVKRNASIDVDTLFAKVIYDLTEKTLSSDQNDLAIYLLQRLKRAKPI
LPSFSSRPSWWNFYDDWSFSEKFFQWIQITGSLGSGSSATVEKAVWLGTPVA
KKTFYGRNNEDFKREVEILAELCHPNITSMFCSPLYRRKCSIIMELMDGDLLALM
QRRLDRNEDHDSPPFSILEVVDIILQTSEGMNYLHEKGIIHRDLKSMNILVKSVKV
TKSEIGYVHVKVADFGLSKTKDSSTRYSNQTWNRGTNRWMAPEVINLGYESTE
GEISFDGKVPKYPLKSDVYSFGMVCYEVLTGDVPFPEEKNPNNVKRMVLEGVR
PDLPAHCPIELKALITDCWNQDPLKRPSFAVICQKLKYLKYLLMTGFSSYQDSYP
STEEPS

A. What are the domains present in this protein?

-Suppose, we are interested in the serine/threonine protein kinase domain.

Obtain more information about it by searching in NCBI's Bookshelf

B. Go back to the CD-Search results page. Obtain a list of proteins with similar domain architecture by clicking on the "Search for similar domains architectures" button. To display the records, click on the links to the subsets of sequences and from there on the “Look up Sequences in Entrez”. Change the display from “Summary” to “FASTA”.

C. Go back to the CD-Search results page. Click on the “Full Report” radio button. Generate a multiple sequence alignment for the top 10 sequences representative of the conserved domain hit by clicking on the graphic representation of the serine/threonine kinase domain from CDD (CDD|00180, the second pink graphic link from the top). Use the "Aligned Rows" list box pull down menu to specify "up to 5" sequences and invoke Cn3D with a display of a 3D modeling template and a multiple sequence alignment including your query sequence by pressing the "Structure View" button.

To show only one top structure, click on the down arrow key. For better view of the backbone, remove the side chains globally (Style--Edit global style--Protein side chains). The query protein contains a serine/threonine protein kinase active-site signature (IIHRDLKSMNILV) where K is the ATP binding site. Identify these residues in the query protein and highlight the corresponding lysine residue in the first protein sequence.

Display the side chains of this residue (Use Style--Annotate--New--Edit Style. Change the protein backbone Rendering to Tubes, Color Scheme to User Selection and User Color to choose the color for the highlighted residue, for example yellow. Repeat these steps for the Protein Side chains row and click the Protein Side chains on. Click on the “Done” button. To zoom in, press z on the keyboard. Note the heterogen near the conserved lysine residue.

D. To obtain the structural neighbors for the serine/threonine protein kinase protein, first click on the top structure entry link 1F3M_C of the similar protein from the CD-Browser page. Next, click on the structure link on the bottom right side, then on the 1F3M header for the record, and finally on the grey “chain C” graphic. Select one or more of the check boxes next to the structure neighbors and download the structures by clicking on the "View 3D Alignment" button.